YESCARTA®
(axicabtagene ciloleucel) Dispersion for infusion

Important Safety Information for Healthcare Providers (HCPs) to Minimise the Risks of Cytokine Release Syndrome (CRS) and Serious Neurologic Adverse Reactions

Healthcare Provider Educational Material: Kite YES IL CRS/NAR: V1 12-11-2020
APPROVED BY THE MINISTRY OF HEALTH ON MAY 2021

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADL	Activities of daily living
CD	Cluster of differentiation
CRS	Cytokine release syndrome
CVVHD	Continuous veno-venous haemodialysis
DLBCL	Diffuse large B-cell lymphoma
FiO2	Fraction of Inspired Oxygen
HCP	Healthcare provider (s)
HLH/MAS	Haemophagocytic lymphohistiocytosis/macrophage activation syndrome
IV	Intravenous
PAC	Patient Alert Card
PMBCL	Primary Mediastinal Large B-cell lymphoma

1. INDICATION

YESCARTA is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

Limitation of Use: YESCARTA is not indicated for the treatment of patients with primary or secondary central nervous system lymphoma.

YESCARTA administration can result in severe, life-threatening, and fatal reactions like cytokine release syndrome (CRS) and serious neurologic adverse reactions.

YESCARTA will only be supplied to hospitals and associated centres that are qualified and only if the healthcare providers (HCPs) involved in the treatment of a patient have completed training on the HCP educational material, and have on-site, immediate access to tocilizumab.

To mitigate the safety risks associated with YESCARTA (axicabtagene ciloleucel) treatment, clinical facilities must be specifically qualified prior to ordering YESCARTA.

2. PURPOSE OF THE EDUCATIONAL MATERIAL

This guide is intended to provide information on reporting serious adverse reactions of CRS and serious neurologic adverse reactions associated with YESCARTA, including guidance on monitoring for CRS, neurologic adverse reactions. Other adverse reactions include infections and febrile neutropenia, prolonged cytopenias and hypogammaglobulinaemia. The educational material will focus on how to manage symptoms associated with CRS and serious neurologic adverse reactions. Healthcare providers are asked to report any suspected adverse reactions. All patients or their caregivers must be given a Patient Alert Card (PAC) by their HCP to educate them about the symptoms of CRS and serious neurologic adverse reactions and the need to report the symptoms to their treating doctor immediately. Treating HCPs should also advise their patients to keep the PACs with them at all times and show it to any HCP who may treat them.

Review the full Prescribing Information (PI) and the Patient Information Leaflet (PIL) for YESCARTA for a more detailed description of these and other risks. Also read this HCP Educational Material prior to prescribing. This will enable you to understand how YESCARTA is used and will help you to:

- Identify and understand serious adverse reactions of CRS and serious neurologic adverse reactions as well as infections and febrile neutropenia, prolonged cytopenias and hypogammaglobulinaemia
- Appropriately manage the adverse reactions
- Utilise the PAC with patients
- Ensure that adverse reactions are adequately and appropriately reported

The information in this guide is provided by Gilead, for HCPs who are involved in the treatment of patients who receive YESCARTA.

To obtain copies of the patient educational material, contact Gilead Medical Information at medinfo.israel@gilead.com. Also, see YESCARTA leaflet for more information.

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information.

To report an adverse reaction associated with YESCARTA, please contact the Ministry of Health using the link http://sideeffects.health.gov.il or through the registration holder: DrugSafety.Israel@gilead.com.

HOW TO USE THIS GUIDE

This guide will help you to:

- Identify patients with CRS or serious neurologic adverse reactions
- Learn the importance of excluding alternate causes for the reported symptoms
- Grade the severity of the CRS or serious neurologic adverse reactions
- Provide treatment of the CRS or serious neurologic adverse reactions according to the severity grade, as shown in this guide

3. WHAT IS YESCARTA

YESCARTA, an engineered autologous T-cell immunotherapy product, binds to cluster of differentiation (CD) 19-expressing cancer cells and normal B cells. Following anti-CD19 chimeric antigen receptor (CAR)-T cell engagement with CD19-expressing target cells, the CD28 and CD3-zeta co-stimulatory domains activate downstream signaling cascades that lead to T-cell activation, proliferation, acquisition of effector functions, and secretion of inflammatory cytokines and chemokines. This sequence of events leads to apoptosis and necrosis of CD19 expressing target cells. YESCARTA is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and PMBCL, after two or more lines of systemic therapy.

4. IMPORTANT POINTS TO CONSIDER BEFORE YOU ADMINISTER YESCARTA

- To mitigate the safety risks associated with YESCARTA treatment, clinical facilities must be specifically qualified prior to ordering YESCARTA.
- YESCARTA must be administered in a qualified clinical setting. The qualified clinical facility must ensure the availability of at least 4 doses of tocilizumab (an Interleukin-6 receptor inhibitor) per patient prior to the infusion of YESCARTA, for administration within two hours, if required for the treatment of CRS.
- Monitor patients daily for the first 10 days following infusion for signs and symptoms of CRS, neurologic adverse reactions and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs or symptoms of CRS and/or neurologic events. After the first 10 days following the infusion, the patient should be monitored at the physician's discretion.
- Weekly phone calls to the patients by the infusion site HCP for assessments are strongly recommended after the first week of daily monitoring.
- Instruct patients to remain within proximity, no more than 2 hours away, of a qualified clinical facility for at least 4 weeks following infusion.

Due to the risks associated with YESCARTA treatment, infusion should be delayed if a patient has any of the following conditions:

- Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions or hypotension) including from preceding chemotherapies
- Active uncontrolled infection or inflammatory disease
- Active graft versus host disease (GVHD)

YESCARTA should not be administered until these conditions have resolved.

5. GUIDANCE ON MANAGING CYTOKINE RELEASE SYNDROME (CRS)

Table 1. Signs and Symptoms Associated with CRS

CYTOKINE RELEASE SYNDROME	
Any organ can be affected by CRS. The following are common signs and symptoms:	
Pyrexia	Chills
Tiredness	Renal impairment
Cardiac failure	Headache
Tachycardia	Malaise
Cardiac arrhythmias	Transaminitis
Dyspnoea	Nausea
Hypoxia	Diarrhoea
Capillary leak syndrome	Hypotension

Abbreviations: CRS, cytokine release syndrome.

Cytokine release syndrome (CRS) occurred in 93% of patients. Eleven percent (11%) of patients experienced Grade 3 or higher (severe, life threatening and fatal) CRS. The median time to onset was 2 days (range 1 - 12 days) and the median duration (time to resolution) was 7 days (range 2 - 29 days). Ninety-eight percent (98%) of patients recovered from CRS.

The most common signs or symptoms associated with CRS included pyrexia (83%), hypotension (44%), tachycardia (24%), hypoxia (23%), and chills (20%). Serious adverse reactions that may be associated with CRS included acute kidney injury, atrial fibrillation, ventricular tachycardia, cardiac arrest, cardiac failure, capillary leak syndrome, hypotension, hypoxia, and haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS).

Monitor patients daily for the first 10 days following infusion for signs and symptoms of CRS, neurologic adverse reactions and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs or symptoms of CRS and/or neurologic events. After the first 10 days following the infusion, the patient should be monitored at the physician's discretion. Patients should be instructed to remain within proximity, no more than 2 hours away, of a qualified clinical facility for at least 4 weeks following infusion.

YESCARTA should not be administered to patients with active infections or inflammatory disease until these conditions have resolved. Diagnosis of CRS requires excluding alternate causes of systemic inflammatory response, including infection. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated.

Cytokine release syndrome (CRS) has been known to be associated with end organ dysfunction (eg, hepatic, renal, cardiac, and pulmonary). In addition, worsening of underlying organ pathologies can occur in the setting of CRS. Patients with medically significant cardiac dysfunction should be managed by standards of critical care and measures such as echocardiography should be considered.
Haemophagocyticlymphohistiocytosis/macrophage activation syndrome (HLH/MAS) presents with symptoms similar to CRS. Evaluation for HLH/MAS should be considered in patients with severe or unresponsive CRS.

Patients who experience Grade 2 or higher CRS (eg, hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life threatening CRS, consider intensive care supportive therapy.

The administration of tocilizumab and corticosteroids did not result in an observed difference in the pharmacokinetic profile of YESCARTA. Tumour necrosis factor (TNF) antagonists are not recommended for management of YESCARTA associated CRS.

Treatment algorithms have been developed to ameliorate some of the CRS symptoms experienced by patients on YESCARTA (see Table 3 for more details).

Table 2 describes the grading of CRS according to the Lee criteria*:

Table 2. CRS Grading (Excluding Neurologic Adverse Reactions)

Lee Grade	Symptoms
Grade 1	Symptoms require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement < 40% fraction of inspired oxygen (FiO2) or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥ 40% FiO2 or hypotension requiring high dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis
Grade 4	Life-threatening symptoms Requirements for ventilator support or continuous veno-venous haemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis)

* Lee D, Gardner R, Porter D, et al. How I treat: current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124(2):188-195.

Table 3. Categories of CRS Severity and Management

CRS Grade[a]	Supportive Care	Tocilizumab	Corticosteroids	Follow-up
Grade 1 • Symptoms require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)	• Supportive care per institutional standard of care • Closely monitor neurologic status	N/A	N/A	Not improving after 24 hours: • Tocilizumab 8 mg/kg Intravenous (IV) over 1 hour (not to exceed 800 mg)
Grade 2 • Symptoms require and respond to moderate intervention • Oxygen requirement < 40% FiO_2 or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity	• Continuous cardiac telemetry and pulse oximetry as indicated • IV fluids bolus for hypotension with 0.5 to 1.0 L isotonic fluids • Vasopressor support for hypotension not responsive to IV fluids • Supplemental oxygen as indicated	• Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) • Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen; maximum of 3 doses in a 24-hour period. Maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS	• If no improvement within 24 hours after starting tocilizumab, manage per Grade 3	Improving • Manage as above • If corticosteroids were started: continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days Not improving • Manage as Grade 3 (below)
Grade 3 • Symptoms require and respond to aggressive intervention • Oxygen requirement ≥ 40% FiO_2 or hypotension requiring high dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis	• Management in monitored care or intensive care unit	• Per Grade 2	• Methylprednisolone 1 mg/kg IV BID or equivalent dexamethasone (e.g., 10 mg IV every 6 hours)	Improving • Manage as above • Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days Not improving • Manage as Grade 4 (below)
Grade 4 • Life-threatening symptoms • Requirements for ventilator support or continuous veno-venous haemodialysis (CVVHD) • Grade 4 organ toxicity (excluding transaminitis)	• Per Grade 3 • Mechanical ventilation and/or renal replacement therapy may be required	• Per Grade 2	• High-dose corticosteroids: methylprednisolone 1000 mg/day IV x 3 days	Improving • Manage as above • Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days Not improving • Consider adding alternate immunosuppressants

[a] (Lee D, Gardner R, Porter D, et al. How I treat: current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124(2):188-195)

6. GUIDANCE ON MANAGING NEUROLOGIC ADVERSE REACTIONS

Table 4. Signs and Symptoms Associated With Neurologic Adverse Reactions

NEUROLOGIC ADVERSE REACTIONS	
The following are common signs and symptoms:	
Seizures	Ataxia
Somnolence	Memory impairment
Headache	Mental status changes
Confusion	Hallucinations
Agitation	Depressed level of consciousness
Speech disorders	Delirium
Tremor	Dysmetria
Encephalopathy	

Neurologic adverse reactions occurred in 67% of patients in a study, 32% of patients experienced Grade 3 or higher (severe or life threatening) adverse reactions. The median time to onset was 5 days (range: 1 - 17 days). The median duration (time to duration) was 13 days (range: 1 - 191 days). Four patients died of other causes prior to resolution of their neurologic adverse reactions. Most patients recovered from neurologic adverse reactions, with the exception of 4 patients who had ongoing neurologic reactions at the time of death; the deaths were due to other causes.

The most common signs or symptoms associated with neurologic adverse reactions included encephalopathy (58%), headache (40%), tremor (31%), dizziness (21%), aphasia (18%) and delirium (17%). Serious adverse reactions including encephalopathy (22%), aphasia (4%), delirium (4%) and seizures (1%) have been reported in patients administered YESCARTA. Serious and fatal cases of cerebral oedema have occurred in patients treated with YESCARTA.

Other neurologic adverse reactions have been reported less frequently in clinical trials and included dysphagia (5%), myelitis (0.2%), and quadriplegia (0.2%).

Spinal cord oedema was reported, in the context of neurologic toxicity, in the post marketing setting.

There is limited experience with YESCARTA in patients with lymphomas involving the central nervous system (CNS). Patients with a history of CNS disorders such as seizures or cerebrovascular ischaemia may be at increased risk. YESCARTA is not indicated for the treatment of patients with primary or secondary central nervous system lymphoma.

Patients should be monitored at least daily for 10 days at the qualified healthcare facility following infusion for signs and symptoms of neurologic toxicity. After the first 10 days following the infusion, the patient should be monitored at the physician's discretion.

Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive care supportive therapy for severe or life threatening neurologic toxicities. Treatment algorithms have been developed to ameliorate the neurologic adverse reactions experienced by patients on YESCARTA (see Table 5 for more details). Patients should be instructed to remain within proximity, no more than 2 hours away, of a qualified clinical facility for at least 4 weeks following infusion to monitor for signs and symptoms of neurologic adverse reactions. Counsel patients to seek immediate medical attention should signs or symptoms of neurologic adverse reactions occur at any time.

Table 5. Grading and Management of Neurologic Adverse Reactions

Neurologic Adverse Reaction (Grading Assessment CTCAE 4.03)	Supportive Care	Concurrent CRS	No Concurrent CRS[c]	Follow-up
Grade 1 Examples include: • Somnolence—mild drowsiness or sleepiness • Confusion—mild disorientation • Encephalopathy-mild limiting of activities of daily living (ADLs) • Dysphasia—not impairing ability to communicate	• Supportive care per institutional standard of care • Closely monitor neurologic status • Consider prophylactic non-sedating, antiseizure medication e.g., levetiracetam	N/A	N/A	Not improving • Continue supportive care
Grade 2 Examples include: • Somnolence—moderate, limiting instrumental ADLs • Confusion—moderate disorientation • Encephalopathy—limiting instrumental ADLs • Dysphasia—moderate impairing ability to communicate spontaneously • Seizure(s)	• Continuous cardiac telemetry and pulse oximetry as indicated • Closely monitor neurologic status with serial neuro exams to include fundoscopy and Glasgow Coma Score. Consider neurology consult • Perform brain imaging (e.g., magnetic resonance imaging (MRI), electroencephalogram (EEG), and lumbar puncture (with opening pressure) if no contraindications • Consider prophylactic non-sedating, antiseizure medication	Concurrent CRS • Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) • Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen; maximum of 3 doses in a 24-hour period. Maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS. If no improvement within 24 hours after starting tocilizumab administer dexamethasone[a] 10 mg IV every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days	No concurrent CRS • Dexamethasone at 10 mg IV every 6 h. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days	Improving • Manage as above • Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days Not improving • Manage as Grade 3 (below)

Table 5. Grading and Management of Neurologic Adverse Reactions (continued)

Neurologic Adverse Reaction (Grading Assessment CTCAE 4.03)	Supportive Care	Concurrent CRS	No Concurrent CRS[c]	Follow-up
Grade 3 Examples include: • Somnolence—obtundation or stupor • Confusion—severe disorientation • Encephalopathy—limiting self-care ADLs • Dysphasia—severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly	• Per Grade 2 • Management in monitored care or intensive care unit	• Administer tocilizumab per Grade 2 • In addition, administer dexamethasone 10 mg IV with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days	• Dexamethasone at 10 mg IV every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days	Improving • Manage as above • Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days Not improving • Manage as Grade 4 (below)
Grade 4 • Life-threatening consequences • Urgent intervention indicated • Requirement for mechanical ventilation • Consider cerebral oedema	• Per Grade 3 • Mechanical ventilation may be required	• Administer tocilizumab per Grade 2 • In addition, administer methylprednisolone 1000 mg/day IV x 3 days; if it improves, then manage as above	• High-dose corticosteroids: Administer methylprednisolone[b] 1000 mg/day IV x 3 days; if it improves, then manage as above	Improving • Manage as above • Continue methylprednisolone use until the event is Grade 1 or less, then taper over 3 days Not improving • Consider alternate immuno-suppressants

[a]Or equivalent methylprednisolone dose (1 mg/kg).

[b]Equivalent dose of dexamethasone is 188 mg/day.

[c]No concurrent CRS: Tocilizumab not indicated.

7. INFECTIONS AND FEBRILE NEUTROPENIA

Febrile neutropenia was observed in 36% of patients after YESCARTA infusion. Infections occurred in 39% of patients in ZUMA-1. Grade 3 or higher (severe, life-threatening, or fatal) infections occurred in 26% of patients. Grade 3 or higher unspecified pathogen, bacterial, and viral infections occurred in 19%, 9%, and 6% of patients respectively. The most common site of infection was in the respiratory tract.

Monitoring and management guidance

Serious infections have been very commonly observed with YESCARTA. Patients should be monitored for signs and symptoms of infection before, during, and after YESCARTA infusion and treated appropriately. Prophylactic anti microbials should be administered according to standard institutional guidelines. Febrile neutropenia has been observed in patients after YESCARTA infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

8. PROLONGED CYTOPENIAS

Grade 3 or higher neutropenia (including febrile neutropenia), anaemia, and thrombocytopenia occurred in 80%, 45%, and 40% of patients, respectively. Prolonged (still present at Day 30 or with an onset at Day 30 or beyond) Grade 3 or higher neutropenia, thrombocytopenia, and anaemia occurred in 26%, 24%, and 10% of patients, respectively. Grade 3 or higher neutropenia, thrombocytopenia, and anaemia present after Day 93 occurred in 11%, 7%, and 3% of patients, respectively.

Management guidance

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA infusion. Grade 3 or higher prolonged cytopenias following YESCARTA infusion occurred very commonly and included thrombocytopenia, neutropenia, and anaemia. Monitor blood counts after YESCARTA infusion.

9. HYPOGAMMAGLOBULINAEMIA

In ZUMA 1, hypogammaglobulinaemia occurred in 16% of patients. Cumulatively, 33 (31%) of 108 subjects received intravenous immunoglobulin therapy at the time of the 24 month analysis.

Management guidance

B cell aplasia leading to hypogammaglobulinaemia can occur in patients receiving treatment with YESCARTA. Hypogammaglobulinaemia has been very commonly observed in patients treated with YESCARTA. Immunoglobulin levels should be monitored after treatment with YESCARTA and managed using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement.

10. POST YESCARTA INFUSION MONITORING

Post YESCARTA infusion recommendations:

- Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic adverse reactions and other toxicities.
- Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs or symptoms of CRS and/or neurologic adverse reactions.
- Patients stay within proximity (no more than 2 hours away) of the qualified clinical facility so that they can be monitored for signs and symptoms of CRS and neurologic adverse reactions.
- Treating HCPs should make weekly phone calls to assess for any signs or symptoms suggestive of CRS and neurologic adverse reactions.
- If the patients develop any signs or symptoms of CRS or neurologic adverse reactions, they should be instructed to immediately go to the qualified clinical facility (or nearest hospital if travel is deemed unsafe) for evaluation for hospitalisation and treatment which includes supportive care and use of tocilizumab and/or corticosteroids.

Below is a checklist of some of the signs and symptoms that the HCP should assess for during weekly calls to the patient. This checklist is not meant to be all-inclusive. Based on the responses below, the decision to bring the patient for evaluation will be at the discretion of the treating physician.

GENERAL	YES	NO
Do you have a fever?		
Do you have any chills?		
Do you have any nausea or vomiting?		
Are you having difficulty sleeping?		
Are you having problems staying awake?		
Are you lightheaded or experiencing dizziness?		
Do you have headaches?		
Do you have loss of balance or coordination?		
Do you have difficulty in speaking or slurred speech?		
Do you have confusion or disorientation?		
Do you have any unusual body movements?		
Do you have dizziness when you stand up?		
Do you have difficulty understanding numbers or doing math?		
Do you have difficulty writing?		
Do you have shortness of breath or rapid breathing?		
Are you having difficulty breathing?		
Do you have palpitations?		
Are you more tired than you were before Yescarta infusion?		

11. PATIENT COUNSELLING

Talk to the patient about the risk of CRS and neurologic adverse reactions. Early diagnosis and appropriate management of CRS and neurologic adverse reactions are essential to minimise life threatening complications. Remind the patient not to treat their own symptoms. Instruct patients to contact their HCP and/or seek immediate care if they experience any signs and symptoms associated with CRS and/or neurologic adverse reactions, which include:

- Fever (eg, temperature above 38°C)
- Difficulty breathing
- Chills or shaking chills
- Confusion
- Decreased level of consciousness
- Seizures
- Tremors
- Dizziness or lightheadedness
- Severe nausea, vomiting, or diarrhoea
- Fast or irregular heartbeat
- Severe fatigue or weakness

Provide the YESCARTA PAC to the patient or the patient's caregiver. Tell the patient to carry the PAC at all times and to share the PAC with any HCP involved in the patient's treatment.

After YESCARTA infusion advise patients to stay within proximity (no more than 2 hours away) of a qualified clinical facility for a minimum of 4 weeks to monitor for signs and symptoms of CRS or neurologic adverse reactions.

12. REPORTING OF ADVERSE REACTIONS

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

HCPs are asked to report any suspected adverse reactions associated with YESCARTA.

Please contact the Ministry of Health using the link **http://sideeffects.health.gov.il** or through the registration holder: **DrugSafety.Israel@gilead.com.**